Most recommended medical interventions reach P<0.005 for their primary outcomes in meta-analyses

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Abstract: Background: It has been proposed that the threshold of statistical significance should shift from P-value < 0.05 to P-value < 0.005, but there is concern that this move may dismiss effective, useful interventions. We aimed to assess how often medical interventions are recommended although their evidence in meta-analyses of randomized trials lies between P-value = 0.05 and P-value = 0.005. Methods: We included Cochrane systematic reviews (SRs) published from 1 January 2013 to 30 June 2014 that had at least one meta-analysis with GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment and at least one primary outcome having favourable results for efficacy at P-value < 0.05. Only comparisons of randomized trials between active versus no treatment/placebo were included. We then assessed the respective UpToDate recommendations for clinical practice from 22 May 2018 to 5 October 2018 and recorded how many treatments were recommended and what were the P-values in their meta-analysis evidence. The primary analysis was based on the first-listed outcomes. Results: Of 608 screened SRs with GRADE assessment, 113 SRs were eligible, including 143 comparisons of which 128 comparisons had first-listed primary outcomes with UpToDate coverage. Altogether, 60% (58/97) of interventions with P-values < 0.005 for their evidence were recommended versus 32% (10/31) of those with P-value 0.005-0.05. Therefore, most (58/68, 85.2%) of the recommended interventions had P-values < 0.005 for the first-listed primary outcome. Of the 10 exceptions, 4 had other primary outcomes with P-values < 0.005 and another 4 had additional extensive evidence for similar indications that would allow extrapolation for practice recommendations. Conclusions: Few interventions are recommended without their evidence from meta-analyses of randomized trials reaching P-value < 0.005. Keywords: P-value; Cochrane; UpToDate; meta-analysis; recommendation; statistical threshold.

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ABSTRACT

BACKGROUND

It has been proposed that the threshold of statistical significance should shift from P-value<0.05 to P-value<0.005, but there is concern that this move may dismiss effective, useful interventions. We aimed to assess how often medical interventions are recommended although their evidence in meta-analyses of randomized trials lies between P-value=0.05 and P-value=0.005.

METHODS

We included Cochrane systematic reviews (SRs) published from 01/01/2013 to 06/30/2014 that had at least one meta-analysis with GRADE assessment and at least one primary outcome having favorable results for efficacy at P-value<0.05. Only comparisons of randomized trials between active versus no treatment/ placebo were included. We then assessed the respective UpToDate recommendations for clinical practice from 05/22/2018 to 10/05/2018 and recorded how many treatments were recommended and what were the P-values in their meta-analysis evidence. The primary analysis was based on the first-listed outcomes.

RESULTS

Of 608 screened SRs with GRADE assessment, 113 SRs were eligible, including 143 comparisons of which 128 comparisons had first-listed primary outcomes with UpToDate coverage. Altogether, 60% (58/97) of interventions with P-values<0.005 for their evidence were recommended versus 32% (10/31) of those with P-value 0.005-0.05. Therefore, most (58/68, 85.2%) of the recommended interventions had P-values<0.005 for the first-listed primary outcome. Of the 10 exceptions, 4 had other primary outcomes with P-values<0.005 and another 4 had additional extensive evidence for similar indications that would allow extrapolation for practice recommendations.

CONCLUSIONS

Few interventions are recommended without their evidence from meta-analyses of randomized trials reaching P-value<0.005.

STUDY REGISTRATION

Center for Open Science, Open Science Framework: https://osf.io/4phzy/.

Keywords: P-value, statistical threshold, recommendation, meta-analysis, Cochrane, UpToDate

KEY MESSAGES

- Among treatments that have evidence summarized in meta-analyses of randomized trials and that are also recommended, the large majority reach $P<0.005$ in primary outcomes for their evidence.
- In most of the exceptions landing between $P= 0.05$ and 0.005, there is additional extensive evidence that would allow for recommendations.
- Clinical and statistical significance are different concepts and statistical significance may not suffice for recommending an intervention but requiring at least $P<0.005$ for statistical significance seems reasonable, as it will not result in many recommended interventions being discarded.

Introduction

Thresholds are widely used by researchers and authors to claim statistical significance and to interpret research findings[1,2]. The most commonly reported threshold is that of "P-value<0.05". However, the use and misuse of P-values to determine the effectiveness of an intervention has received a great amount of criticism. P-values alone do not prove the clinical relevance of the effect[3]. Use of thresholds that claim statistical significance of the results do not fully substantiate effectiveness of a treatment for clinical practice or vice- versa, although statistical significance is used to inform clinical significance. For example, a non- significant finding for an intervention of interest does not necessarily mean that the effect of this treatment is not clinically meaningful as non- optimal sample sizes or low event rates may overshadow the true effect[4–6].

Following the 2016 statement on P-values by the American Statistical Association (ASA)[7], discussions have been rekindled about how to improve the use of statistical inference tools. One possibility is to just abandon P-value thresholds entirely[8], since they are so widely misused and misinterpreted. However, simply maintaining P-values without thresholds may cause statistical anarchy in the largely statistically-undertrained community of researchers[9]. Current lack of training impedes the widespread adoption of possibly better alternatives e.g. Bayesian or false-discovery rate approaches. Moreover, P-value thresholds have already been widely, almost ubiquitously, used in past published papers, including randomized trials and meta-analyses thereof. One proposal is to lower the routinely used P-value threshold from 0.05 to 0.005 to claim statistical significance with P-values 0.005-0.05 being merely "suggestive"[10,11]. Endorsement of lower thresholds would reduce "positive" results and may thus decrease false-positives, since P=0.005 confers almost a 10-fold larger Bayes factor against the null than P=0.05. The shift to the more conservative P-value threshold may also encourage the conduct of fewer, well-designed and larger studies with increased power to satisfy these thresholds. The effects of the

currently used statistical standards on the credibility of research claims are not confined to biomedical science[10]. Empirical evidence shows that research from disciplines other than medicine or genetic epidemiology may bear substantial gains if they adopt more stringent levels of statistical significance to substantiate their claims. Some reports that come from studies on psychology[12] or experimental economics[13] reveal a nearly double rate of replication of these studies given the adoption of $P<0.005$, compared to P- value between 0.05 and 0.005.

However, counterarguments also exist [14,15]. A more stringent threshold may discard true-positive results, cultivate more extreme selective outcome reporting and promote use of surrogate endpoints (that more easily reach lower P-values).

For clinical studies that are already completed and reported and for the assessment of their evidence, the choice of threshold pertains mostly to the trade-off between false-positives and true-positives. Results of individual trials are typically included in meta-analyses and these are used eventually for recommendations for practice. Ideally, one wants to recommend effective, useful interventions and avoid recommending those that are not effective or useful. Statistical significance of the evidence is one among many considerations influencing treatment recommendations, and careful assessment of the quality/strength of the evidence (e.g., as appraised by Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) [16,17] is pivotal. Regardless, while clinical significance is a much broader construct than statistical significance, it would be useful to understand empirically what levels of statistical significance are currently linked to recommendations for clinical use.

Here, we identified the P-value of the evidence for primary efficacy outcomes for various treatments that had reached the traditional statistical significance (P-value<0.05) in Cochrane meta-analyses in various

fields of medicine. We aimed to assess whether lowering the P-value threshold by one decimal point to 0.005 would discard many treatments that are clearly recommended.

Methods

Protocol Registration

The protocol for this meta-epidemiological study was developed and *a priori* registered in the Center for Open Science, Open Science Framework (osf: https://osf.io/4phzy/).

Study Selection and Eligibility criteria

We considered all Cochrane Database of Systematic Reviews (CDSR) systematic reviews (SRs) published from January 1, 2013, to June 30, 2014 from the CDSR, a set that we had also used in previous work[18]. We searched for newer updated versions of these reviews published until May 2018; whenever such versions existed, we used the most updated version.

We used SRs including at least one comparison (meta-analysis) with GRADE assessment and at least one primary outcome having favorable statistically significant results at P-value<0.05 for efficacy/effectiveness, or equivalently excluding the null in the 95% confidence interval (CI). We only kept comparisons between treatment (active) versus no treatment/placebo, rather than head-to-head comparisons between different active treatments (head-to-head compared treatments may both be very effective and recommended, but their differences may be negligible and non-significant). When different active treatments versus no treatment/placebo comparisons were included in the same SR, they were considered separately.

SRs and comparisons within SRs were excluded when they did not report any primary outcome with P-value<0.05 and when they had primary outcomes with P-value<0.05 favoring the no treatment/placebo

arm. Comparisons including primary studies other than randomized controlled trials (RCTs) were excluded. Primary outcomes that pertained to toxicity/harms from therapy were also excluded.

Data Extraction

Data were extracted on SR level, on comparison (i.e., intervention) level as well as on outcome level, forming a 3-level hierarchical structure for the dataset. Our aim was to embrace all levels of information, as there might be >1 primary outcome per comparison recorded, or >1 comparison for the same SR. At the SR level, we extracted: author, year, country, and region of publication, whether the review was new or an update, Cochrane group involved (as an indicator of medical domain), SR type (interventional, diagnostic). At the comparison level, every comparison comprising of treatment vs no treatment/placebo within the same SR was considered eligible, and information on the category of the intervention (including surgical, pharmacologic, behavioral or medical treatments, and diet or exercise interventions) was obtained. On the outcome level, we recorded: type of outcome [objective (mortality or outcomes assessed with an instrument or preset measurable criteria) or subjective], subtype of outcome (mortality, pain, quality of life, other), quality of the evidence according to GRADE (very low, low, moderate, high), number of studies included, effect size metric (odds ratio, risk ratio, risk difference, mean difference, standardized mean difference, other), point estimate (the summary effect as per SR authors' decision to analyze using either random or fixed effects), 95% CI and exact P-value (when not reported, we calculated it from the effect size and 95% CI). Additionally, and on an exploratory basis, we extracted data on between-study heterogeneity I^2 and between-study variance.

Recommendations for practice were extracted from UpToDate chapters between May 22nd, 2018 and October 5th, 2018[19] on recorded treatments/interventions from the included SRs. We recorded whether a treatment modality was clearly recommended, described as an option in some circumstances, not

recommended, or recommended against. While we originally anticipated that it would have been useful to record also the relative prioritization of recommended treatments (e.g., first-line, second-line, etc.), in-depth examination of UpToDate showed that this gradation is rarely stated, while it is typically discernible whether a treatment is clearly recommended or recommended as an option under some circumstances.

Main Outcomes and Statistical Analyses

The proportion of P-values ranging from 0.05 to 0.005 were recorded from the distribution of P-values (P-curve) for all eligible comparisons, using the first listed primary outcome in the GRADE summary of findings (SoF) tables in the SRs when multiple eligible primary outcomes existed. In each case, we assessed which interventions were in the border zone (P-value 0.05 to 0.005) and were clearly recommended for clinical use. We examined whether the proportion of recommended treatments was different in P-value strata (<0.005 versus 0.005-0.05). Further, we also assessed separately the more granular categories (clearly recommended, option in some circumstances, not recommended, recommended against) in terms of their distributions of P-values. The primary analysis was based on the first-listed outcomes across all comparisons within the SRs. Whenever we identified outcomes in the opposite direction to the primary (first-listed) one for the same comparison, these were assigned a P-value=1.00.

Cross-tabulations were conducted for the association between the P-value category (0.005-0.05 or <0.005) and recommendation category, intervention, outcome type/ subtype, GRADE category, amount of heterogeneity (I^2<50% or >=50%), and tertiles of sample size. Pearson chi-squared and Fisher's exact tests were conducted as appropriate. On an exploratory basis, we undertook an ordinal logistic regression for the effect of P-value (0.005-0.05 or <0.005) and GRADE on recommendation.

Sensitivity Analyses

We conducted sensitivity analyses using only the highest, only the lowest, and only the geometric mean P-value from each eligible comparison, when multiple eligible primary outcomes were identified.

Furthermore, analyses were conducted where all comparisons were re-analyzed using random effects models. We accessed statistical data of each SR through the Cochrane Library and the respective RevMan files.

Analyses were performed with STATA version 15.1 software (Stata Corporation, College Station, Tex, USA).

Results

From an initial pool of 1,394 SRs across all medical domains and covering 18 months, we had previously identified 608 SRs with included GRADE evaluations, routinely within SoF Tables. Of these, 113 fit the pre-determined inclusion criteria, encompassing 143 eligible comparisons of active versus no treatment/placebo, and 128 of those treatments/indications had been covered by UpToDate (Figure 1). Characteristics of topics and outcomes are presented for those with P-value 0.005-0.05 and those with P<0.005 (Table 1).

Primary Analysis

For the 128 first listed primary outcomes of treatments that were covered by UpToDate, only 31 (24.2%) reported a P-value between 0.05 and 0.005. Altogether, 60% (58/97) of the interventions with P-values<0.005 for their evidence were recommended versus 32% (10/31) of those with P-value 0.005-0.05 (odds ratio=3.12; 95% CI 1.34, 7.24; p=0.008). Most (58/68, 85.2%) of the recommended interventions had P-values<0.005 in the first listed primary outcome. The respective proportions were 16/22 (72.7%) for optional interventions, 17/25 (68.0%) for the not recommended interventions, and 6/13 (46.2%) for interventions recommended against. High level of evidence according to GRADE was

seen in 23/97 (23.7%) of P-values<0.005 and 3/31 (9.7%) of P-values 0.005-0.05 (odds ratio=2.90; 95% CI 0.85, 9.73; p=0.09).

Since both P-value and GRADE might be taken into consideration when making recommendations for practice, we considered both of them in a logistic regression. The odds of a treatment being recommended increased 2.75-fold with P-value<0.005 (95% CI 1.26, 6.02) after adjusting for GRADE (Table 2).

When multiple outcomes were available (n=65 topics), for only one topic was one of them statistically significant in the opposite direction than the first listed primary outcome. This pertained to the risk for pneumonia after the use of combined inhalers for chronic obstructive pulmonary disease.

Sensitivity Analysis

The association of P-value <0.005, rather than 0.005-0.05, with recommended interventions remained similar when we examined the lowest P-value across multiple eligible outcomes for each eligible comparison, the highest P-value, or the geometric mean of the P-values (Supplementary Table 1).

When we calculated the P-Values for all eligible first-listed outcomes by random effects estimates of the summary measures, the overall picture was very similar. The number of treatments that were recommended based on the standard P-value threshold of <0.05 (but not <0.005) increased only by 5 (Supplementary Table 2). Results remained similar for the lowest, the highest, and the geometric means of P-values according to random effects (Supplementary Table 3).

Recommendations despite P>=0.005

Based on our primary analysis, we recorded 10 first listed outcomes where the active treatments were recommended for clinical practice and where the reported summary of the evidence had a P-value in the

zone of 0.05 and 0.005, thus not conforming to the proposed rule of having P-value<0.005 (Table 3). Of those, 4 comparisons reported a P-value for another examined efficacy outcome (apart from the first listed) that was <0.005. These treatments pertained to vaccines (oral Ty21a) for preventing typhoid fever[20], supplementation with folic or folinic acid for methotrexate receiving rheumatoid arthritis patients[21], oral antibiotics for chronic obstructive pulmonary disease[22], and zolmitriptan for cluster headache[23]. The remaining 6 were isoniazid for post solid organ transplant tuberculosis[24], Doppler ultrasound for pregnant women[25], H2-receptor antagonists for gastro-oesophagyal reflux or endoscopy[26], praziquantel for *Schistosoma mansoni* infection[27], and pre-emptive treatment for cytomegalovirus viraemia in solid organ transplant recipients[28] (Table 3). With the exception of Doppler ultrasound in pregnancy and praziquantel for *Schistosoma mansoni*, the interventions had been extensively tested for other similar indications (isoniazid has been tested for many prophylaxis settings; H2-receptor antagonists have been used extensively to relief symptoms in various settings; and pre-emptive CMV treatment has been used in many immunosuppressed and transplant groups).

Using random effects calculations, 4 of the 5 additional interventions with P-value 0.005-0.05 were related to smoking cessation assessed in specialized settings (post-depression, pre-operatively, workplace)[29–31]. Smoking cessation has far more evidence across diverse settings. The last intervention was maintenance with all-trans retinoic acid/arsenic trioxide for acute promyelocytic leukemia[32], which is associated with a very large effect and is classic, highly-cited intervention in hematology.

In all, the vast majority of treatments bearing evidence summarized in meta-analyses of RCTs and being recommended for use, reached P<0.005 in their primary outcomes. A few exceptions were easily explained.

Discussion

We found that among treatments that have evidence summarized in meta-analyses of randomized trials in the CDSR and reach P-value<0.05 for their first listed primary outcome, only about a quarter do not reach also P-value<0.005. Furthermore, few of those that are recommended by UpToDate do not reach P-value<0.005. Those that are recommended, but do not reach that more conservative level of statistical significance almost always have some other primary outcome (other than the first listed) that reaches P-value<0.005, or they have additional extensive evidence for similar indications. In our series of examined treatments, only two interventions had no P-values<0.005 for any primary efficacy outcome and the examined outcome and had also no or little other favorable evidence for similar indications. Praziquantel for *S. mansoni*[27] is not so highly statistically significant, however, it has a large treatment effect (risk ratio=3.13). Moreover, if indications were to be extended to other parasites besides *S. mansoni*, praziquantel does show effectiveness also against other types of schistosomiasis, clonorchiasis, opisthorchiasis, tapeworm infections, cysticercosis, hydatid disease, and other fluke infections. Finally, ultrasound during pregnancy is a safe and simple intervention recommended for use, even if the P-value for the evidence on reducing perinatal deaths is not that low[25]. In all, moving the P-value threshold to 0.005 would not result in many recommended treatments being "discarded". In addition, nearly 2/3 of the treatments where outcomes that "surpassed" the P-value<0.005 threshold, were actually recommended for clinical practice. Thus, in terms of a cost- benefit evaluation of the proposed threshold, the results of this empirical study show evidence of matching of the new threshold to clinical decision making, when statistical assessment of the findings is considered, without risking loosing otherwise recommended treatment modalities.

We are aware of only one other empirical study that evaluated the 0.05 versus 0.005 threshold for published clinical evidence, focusing on the results of RCTs (not of meta-analyses, as we did) in major medical journals[33]. The authors evaluated 272 primary outcomes from 203 RCTs and recorded 174

outcomes with a P-value<0.05. They found that shifting the threshold of significance to 0.005 would affect 51 of 174 outcomes (29.3%). Across the entire biomedical literature indexed in PubMed, about a third of the papers that claim statistically significant results would fit to the 0.005-0.05 bin[34], but the impact on decision making and recommendations for clinical practice has not been evaluated.

There is extensive theoretical and other work criticizing the use and misuse of P-values and statistical significance[1,7,15,35–39]. Examples of P-value misuse are outcome switching or selective outcome reporting practices based on the perceived significance of the outcome of interest. Should the adoption of lower P-value thresholds be upheld, attention must be drawn to the use of surrogate outcomes that may pass the threshold more easily, since these may be prioritized by researchers, in an attempt to retrieve findings that satisfy the new threshold[40,41]. For this reason, some argue abandoning statistical significance thresholds or even P-values in most applications, and enhancing focus on effect sizes and their uncertainty and other inferential tools e.g. Bayes factors[42,43] and false-discovery rates[44,45]. However, given that P-values are still so widely used and practically ubiquitous in the published literature, it will take continuous, extensive training of the scientific workforce to achieve drastic changes.

RCTs and their meta-analyses guide clinical practice and inform clinicians on treatment decisions. The fact that almost all recommended interventions have P<0.005 for their evidence on the same or similar indications does not diminish the need to place evidence into the appropriate context for each patient. This includes the postulated magnitude of benefits and harms in the specific patient being considered and the specific setting, as well as cost and convenience, and alternative options and their merits and drawbacks. In addition, the fact that we also found a non- negligible amount of treatments having a P<0.005 and not being recommended for clinical practice, at least within the electronic source we used, upholds the claims about the necessity for disentanglement between statistical and clinical significance[5]. This was further elucidated by our primary analysis findings which demonstrated that a very low P-

value for an outcome of interest could also be followed by a recommendation against the treatment provided for clinical practice.

Some limitations should be discussed. First, the P-value derived in a meta-analysis depends on the statistical model used. Our main analysis used the systematic reviewers' choice of statistical methods to summarize data (either fixed or random effects). An analysis using solely calculated P-values by random effects yielded similar patterns. Usually, in the presence of heterogeneity, random effects give estimates with higher P-values[46], but exceptions may occur. Second, we focused on a set of SRs that would give a clean answer for evaluation of the efficacy/effectiveness of treatments versus no treatment/placebo. We excluded any head-to-head comparisons of active interventions that would hinder the determination of the net treatment effects of an intervention. Head-to-head comparisons of active treatments have more complex statistical inferences and decisions may often be based on non-inferiority rather than superiority. Moreover, as network meta-analyses and indirect comparisons become more popular, the indirect evidence may also affect the perception about the effectiveness of a treatment. Additionally, we did not appraise outcomes related to harms or toxicity. Harms are also appraised in different ways to primary efficacy outcomes in RCTs. The use of statistical inferences to substantiate evaluation of outcomes pertaining to adverse effects may be even more problematic or misleading as assessment of harms/ toxicity involves confirming a null effect rather than confirming the presence of an effect

Finally, UpToDate[19] recommendations are not a perfect gold standard. The authors of this resource may express personal opinions. Moreover, some opinions were not easy to categorize using our preconceived categories. UpToDate uses in- house physician editors trained along with the use of GRADE to provide information about the strength of the recommendations for clinical practice[47]. UpToDate frames recommendations around a specific topic or clinical question based on the PICO (participant, intervention, comparator, outcome) format. The recommendations are based on the best available

evidence (preferably from well- designed systematic reviews), while patient values and a cost- benefit trade- off are considered as well. Furthermore, different evidence tools, e.g., guidelines by professional societies or other agencies, may have reached different conclusions and actual extent of clinical use in real life may not fully square with UpToDate recommendations. Nevertheless, we preferred to use UpToDate because it has wide coverage of medicine[48] and it is generally considered to be less affected by bias from professional societies' guidance[49]. A selection bias may exist if UpToDate reviewers focused on discussing preferentially interventions that had evidence with relatively lower P-values. However, we do not believe this is likely, since the recommendations are provided by a panel of in-house trained medical editors based on the best available evidence overall. In addition, it is unlikely that interventions that do not even reach the lenient $P<0.05$ for their evidence on primary outcomes would be recommended.

Allowing for these caveats, we note that clear recommendations favoring the use of a treatment are mostly associated with evidence from RCTs that reach $P<0.005$ when summarized for efficacy in meta-analyses. Asking for a more conservative $P<0.005$ for claiming "statistical significance" would not translate to the overriding of many effective and clearly recommended treatments. Statistical significance (regardless of threshold used) should not be confused with clinical significance: many treatments with very low P-values for some outcomes are still not recommended for clinical use when the broader picture (i.e., patient values and cost- benefit trade- off) is considered. However, the vast majority of interventions that are clearly recommended seem to have substantial statistical support with $P<0.005$.

Competing Interests: None

Contributors: All authors contributed to the design of the study. DK and MS performed data extraction. DK with help from NP, and JI performed statistical analyses. All authors interpreted the data and results. DK wrote the first draft with help from JI and all authors revised the paper and approved the final version. JI is the guarantor. All authors had full access to all of the data.

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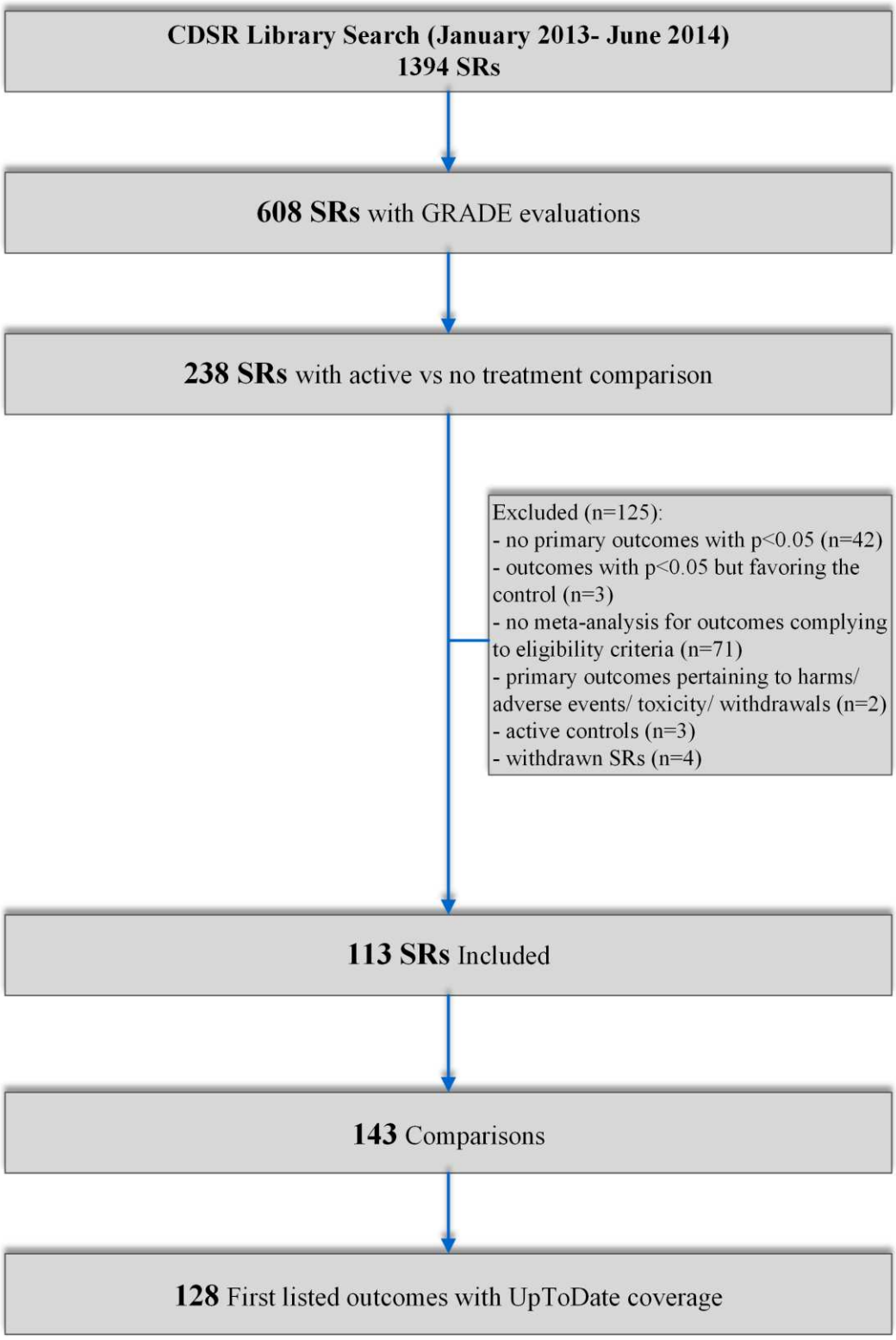
FIGURES

Figure 1. Flow chart of SR selection



TABLES

Table 1. Characteristics according to P-value dichotomized categories (ie, 0.005- 0.05 and <0.005) for the evidence on the first listed primary outcome (n=128 treatments covered also by UpToDate).

	P-value				**Total**		**p-value**
	0.005-0.05		**<0.005**				
	No.	**%**	**No.**	**%**	**No.**	**%**	
Intervention							0.99#
Behavioral/ Medical Device	6	19.4	18	18.6	24	18.8	
Diet/ Exercise	3	9.7	10	10.3	13	10.2	
Pharmacological	22	70.9	69	71.1	91	71.0	
Type of outcome							0.36¥
Objective	17	54.8	44	45.4	61	47.7	
Subjective	14	45.2	53	54.6	67	52.3	
Subtype of Outcome							0.11#
Morbidity	15	48.4	28	28.9	43	33.6	
Mortality	4	12.9	7	7.2	11	8.6	
Pain	4	12.9	31	32.0	35	27.3	
Quality of life	1	3.2	4	4.1	5	3.9	
Other	7	22.6	27	27.8	34	26.6	
I^2 (%)							0.18¥
0- 49	18	58.1	69	71.1	87	68.0	
50- 100	13	41.9	28	28.9	41	32.0	
Sample Size (tertiles)							0.09¥
60- 533	15	48.4	27	27.8	42	32.8	
537- 1378	7	22.6	36	37.1	43	33.6	
1401- 99797	9	29.0	34	35.1	43	33.6	
Total	31	100.0	97	100.0	128	100.0	

¥ Pearson chi- square, # Fisher's exact

Table 2. Ordinal logistic regression for the effect of P-value (treated as binary variable, ie. 0.005-0.05 or <0.005) and GRADE (very low, low, moderate, high) on recommendations for clinical use.

	Odds Ratio	**95% CIs**	**P- value**
P-value			
0.005-0.05	Reference		
<0.005	2.75	1.26, 6.02	0.01
GRADE			0.03[¥]
very low	Reference		
low	3.13	0.98, 10.01	0.05
moderate	4.39	1.51, 12.75	0.007
high	5.74	1.67, 19.69	0.005

[¥] Wald test for GRADE

Table 3. List of the recorded 10 treatments that were recommended by UpToDate and which had P-value 0.005-0.05 for the first-listed outcomes in CDSR reviews.

Disease	**Intervention**	**First Listed Outcome**	**No. outcomes**	**p-primary (1st listed)**
post solid organ transplant tuberculosis	isoniazid	risk of developing TB post-transplant	1	0.027
typhoid fever in adults and children aged 5 years of age and older	oral Ty21a (3 doses)	cases of typhoid fever, year 1	4	0.0093
adults with chronic obstructive pulmonary disease (COPD)	administration of an oral prophylactic antibiotic continuously or intermittently	number of people with one or more exacerbations	3	0.01
pregnant women at increased risk of fetal complications	fetal and umbilical Doppler ultrasound	any perinatal death	1	0.037
adults with cluster headache	intranasal zolmitriptan 5 mg	pain free at 30 min	4	0.015
patients receiving methotrexate for rheumatoid arthritis	supplementation with either folic or folinic acid	incidence of nausea, vomiting or abdominal pain (GI effects)	4	0.0083
gastro-oesophageal reflux disease-like symptoms	H2-receptor antagonists	heartburn	1	0.04
endoscopy negative reflux disease	H2-receptor antagonists	heartburn	1	0.0055
people with *S. mansoni* infection	praziquantel 40 mg/kg	parasitological failure	1	0.044
cytomegalovirus (CMV) disease in solid organ transplant recipients	pre-emptive medication for CMV viraemia	CMV disease	4	0.017

SUPPLEMENTARY TABLES

Supplementary Table 1. P-value threshold by recommendation (sensitivity analysis with minimum p-value, maximum p-value and geometric mean p-value, by comparison), with UpToDate coverage.

P-value threshold	**Recommendation**			
	Recommended Against N (%)	**Not Recommended N (%)**	**Option N (%)**	**Recommended N (%)**
Minimum p-value				
0.005-0.05	5 (21.7)	7 (30.5)	5 (21.7)	6 (26.1)
<0.005	8 (7.6)	18 (17.1)	17 (16.2)	62 (59.1)
Maximum p-value				
0.005-0.05	7 (13.4)	10 (19.2)	11 (21.2)	24 (46.2)
<0.005	6 (7.9)	15 (19.7)	11 (14.5)	44 (57.9)
Geometric mean p-value				
0.005-0.05	6 (20.0)	7 (23.3)	7 (23.3)	10 (33.4)
<0.005	7 (7.1)	18 (18.4)	15 (15.3)	58 (59.2)

Supplementary Table 2. List of the additionally recorded 5 treatments that were recommended by UpToDate and which had P-value 0.005-0.05 for the first-listed outcomes in CDSR reviews, by random effects estimates of the summary measures (sensitivity analysis).

Disease	**Intervention**	**First Listed Outcome**	**No. Outcomes**	**p-primary (1st listed)**
workplace interventions for smoking cessation at least 6 months	pharmacological interventions	smoking cessation	1	0.0083
preoperative smoking cessation	brief behavioral intervention (typically including provision or offer of nicotine replacement therapy)	smoking cessation at time of surgery	1	0.0114
smokers with past depression	psychosocial mood management	smoking cessation: biochemical validation (minority) and self-report follow-up: 6 - 12 months	1	0.04
smokers with past depression	bupropion	smoking cessation: biochemical validation (minority) and self-report follow-up: 6 - 12 months	1	0.04
acute promyelocytic leukemia	any maintenance, eg alltrans retinoic acid (ATRA) or arsenic trioxide (ATO), or combination	disease free survival	2	0.03

Supplementary Table 3. P-value threshold by recommendation (minimum p-value, maximum p-value and geometric mean p-value, by comparison), with UpToDate coverage. Sensitivity analysis with p-values derived from random effects for all comparisons.

P-value threshold	**Recommendation**			
	Recommended Against N (%)	**Not Recommended N (%)**	**Option N (%)**	**Recommended N (%)**
Minimum p-value				
0.005-0.05	6 (18.8)	9 (28.1)	6 (18.8)	11 (34.3)
<0.005	6 (6.5)	15 (16.1)	16 (17.2)	56 (60.2)
Maximum p-value				
0.005-0.05	10 (15.9)	12 (19.1)	13 (20.6)	28 (44.4)
<0.005	2 (3.2)	12 (19.4)	9 (14.5)	39 (62.9)
Geometric mean p-value				
0.005-0.05	7 (18.0)	9 (23.1)	8 (20.5)	15 (38.4)
<0.005	5 (5.8)	15 (17.4)	14 (16.3)	52 (60.5)